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CARDIOVASCULAR RISK AND BLOOD PRESSURE REDUCTION: AN OVERVIEW OF THE OUTCOME TRIALS

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We performed a quantitative overview of the literature to investigate whether properties of antihypertensive drugs may play a role in cardiovascular protection over and beyond blood pressure (BP) lowering. We extracted summary statistics from published articles and computed pooled odds ratios (ORs) for experimental *vs* reference treatment from stratified 2 x 2 contingency tables after application of Zelen's test of heterogeneity. Subsequently, we correlated ORs with BP differences across individual trials, using meta-regression. Among 5 trials in hypertension which compared cardiovascular risk on diuretics or β-blockers with that on calcium-channel blockers (CCBs) or angiotensin-converting enzyme (ACE) inhibitors, all drug classes offered similar cardiovascular protection. However, on CCBs there was more reduction in the risk of stroke (15.1%, CI 2.8–25.9%, p=0.02) and less reduction in the risk of myocardial infarction (20.1%, CI 3.90–38.9%, p=0.01). Meta-regression across 21 trials showed that for cardiovascular mortality the relationship between the ORs and BP differences was linear, whereas for other outcomes there was no further decrease in risk once the systolic/diastolic differences had reached ~15/5 mm Hg. In recent trials of doxazosin *vs* chlorthalidone in hypertensive patients and of ramipril *vs* placebo in high-risk patients, outcome was better on the diuretic and the ACE inhibitor, respectively. However, there were also 2-3/1 mm Hg BP differences between the groups. For systolic BP in the 2 trials, all ORs conformed with the regression lines. For diastolic BP, there was also no separation between predicted (0.99, CI 0.88–1.10) and observed ORs, except for the risk of all cardiovascular events on doxazosin (1.24, CI 1.15–1.33) or ramipril (0.76 CI 0.67–0.85). In conclusion, in the recent trials BP largely accounts for outcome. Older and newer antihypertensive drugs provide similar overall cardiovascular benefit, but CCBs may offer more protection against stroke than myocardial infarction. The hypothesis that ACE inhibitors or α-blockers might influence outcome over and beyond their BP lowering effects remains to be proven.

Key Words: Meta-analysis, Clinical trials, Hypertension

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ANGIOTENSIN II ANTAGONISTS DEMONSTRATE GREATER LONG-TERM PERSISTENCE VERSUS OTHER ANTIHYPERTENSIVE MEDICATIONS

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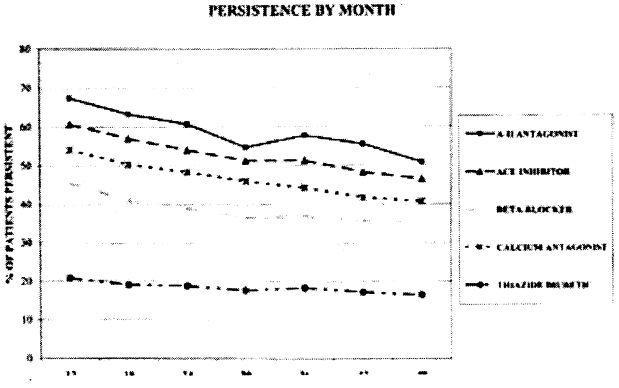
In a previous analysis Bloom (Clinical Therapeutics 1998) demonstrated that losartan, an angiotensin II antagonist (AIIA), had greater 1-year persistence compared to other antihypertensive medications possibly due to the improved tolerability of this new class of agents. To investigate longer-term rates of persistence, the available members of the original Bloom cohort (N=21,723) were identified from the Merck-Medco Managed Care administrative pharmacy claims database and re-analyzed over a 4 year follow-up period (7/01/95-6/30/00).

A cohort of 15,175 patients was continuously benefit eligible over the 4-year follow-up study period, with 451 patients receiving AIIA therapy, 4,428 angiotensin converting enzyme inhibitor (ACE), 3,892 calcium channel blocker (CCB), 3,808 beta-blocker (BB) and 2,596 thiazide diuretic (D) therapy. The cohort had a mean age of 56 years; 28% >65 years of age and 55% were female. Greater persistence by the AIIA class at 12 months (mo) maintained statistical significance (two-sided chi-square, a = 0.05) verses all other classes of antihypertensive agents at 24 mo ($p < 0.007$) and 36 mo ($p < 0.01$). At 48 mo this improved AIIA persistence was statistically significant versus CCB, BB and D ($p < 0.03$) with a statistical trend for ACE ($p = 0.095$). Fewer patients in the BB and D class were persistent at 48 mo with approximately half of the BB and D patients not receiving any hypertensive therapy by the end of the follow-up period. Twenty percent of patients in each therapeutic group switched to another antihypertensive class by year 4, except for D in which 33% of patients switched.

This analysis demonstrates that the superior persistency of the AIIA class at 12-months is maintained for at least 36 and possibly 48 months despite a general decrease in persistency for all agents over time. At the time this analysis was initiated losartan was the only commercially available AIIA and these results may not be generalizable to other AIIA. In conclusion, these findings may have relevance regarding initial agent selection for pharmacologic management of hypertension.



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Key Words: Hypertension Treatment, Persistence, Drug Utilization

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DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER ROTATION OF THE FIVE PRINCIPAL CLASSES OF ANTIHYPERTENSIVE DRUGS

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Outcome studies in hypertension show that achieved BP is more important than choice of initial treatment. Meta-analyses report risk ratios of 1.0 for either calcium blockers (CCB) or ACE inhibitors (ACEi) vs. βblockers (βB) or diuretics (D), but 0.8 for more vs. less intensive reduction in BP by any regimen. We previously reported an open-label rotation through four of the main classes, which demonstrated an approximate doubling of patients controlled on monotherapy after rotation vs. their first drug. We have now completed a more formal study, whose objectives were to demonstrate whether there is true inter-individual response to the classes, and to determine any predictors of resistance to monotherapy.

We studied 25 men and 9 women, aged 28-55 (median 47), with previously untreated hypertension (BP 160±12/101±5 mmHg after 3 readings over 3 months). They received in random order amlodipine 5 mg (CCB), lisinopril 10 mg (ACEi), bisoprolol 5 mg (βB), bendrofluazide 2.5 mg (D), doxazosin (4 mg) (α-blocker) and placebo once daily for